(FILE 'HOME' ENTERED AT 10:46:51 ON 02 JUL 2003)

FILE 'BIOSIS, LIFESCI, JAPIO, USPATFULL, EUROPATFULL, CONFSCI, MEDLINE, CAPLUS' ENTERED AT 10:47:03 ON 02 JUL 2003

L1 40618 S SERINE PROTEASE
L2 42 S L1 AND (MT-SP1)
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L5 1 S L2 AND TISSUE REPAIR

L2 ANSWER 1 OF 42 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AB Membrane type **serine protease** 1 (**MT-SP1**) is a representative member of a large family of related enzymes known as type II transmembrane **serine proteases** or membrane type **serine proteases**. **MT-SP1** has been implicated in the selective proteolysis of key extracellular substrates but its physiological role is still not fully understood. **MT-SP1** expression at the protein and RNA level has been previously examined by nonquantitative methods such as in situ hybridization, Northern blotting and immunohistochemistry. To establish an introductory understanding of the quantitative mRNA expression of **MT-SP1** and to correlate these levels with urokinase-type plasminogen activator receptor (uPAR), a key component of extracellular proteolysis, quantitative RT-PCR was carried out. RNA expression was analyzed in 34 human cancer cell lines, 26 human tissues and 18 primary human breast cancer tissue samples. **MT-SP1** mRNA is highly expressed in many breast, ovarian, prostate and colon cancer cell lines and normal human tissues of endodermal origin. At the transcript level, **MT-SP1** shows a highly statistically significant correlation (Pearson's product moment correlation $r = 0.784$, $p < 0.001$) with uPAR in human breast cancer tissue. The exact role of **MT-SP1** in concert with proteins such as uPAR and other members of the plasminogen activator cascade has yet to be ascertained. However, the significant correlation between **MT-SP1** and uPAR transcript levels in this initial study suggests further work to establish the role of **MT-SP1** as a possible prognostic, diagnostic or therapeutic target for breast cancer.
AN 2003:286553 BIOSIS
DN PREV200300286553
TI Quantitation of membrane type **serine protease** 1 (**MT-SP1**) in transformed and normal cells.
AU Bhatt, Ami S.; Takeuchi, Toshi; Ylstra, Bauke; Ginzinger, David; Albertson, Donna; Shuman, Marc A.; Craik, Charles S. (1)
CS (1) University of California at San Francisco, School of Medicine, 513 Parnassus Ave, Box 0454, San Francisco, CA, 94143, USA USA
SO Biological Chemistry, (February 2003, 2003) Vol. 384, No. 2, pp. 257-266. print.
ISSN: 1431-6730.
DT Article
LA English

L2 ANSWER 2 OF 42 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AB Specific human antibodies targeting proteases expressed on cancer cells can be valuable reagents for diagnosis, prognosis, and therapy of cancer. To this end, a phage-displayed antibody library was screened against a cancer-associated **serine protease**, **MT-SP1**. A protein inhibitor of **serine proteases** that binds to a defined surface of **MT-SP1** was used in an affinity-based washing procedure. Six antibodies were selected on the basis of their ELISA profiles and ability to serve as useful immunological reagents. The apparent Ki, indicative of the potency of the antibodies at inhibiting human **MT-SP1** activity, ranged from 50 pM to 129 nM. Two of the antibodies had approximately 800-fold and 1500-fold selectivity when tested against the most homologous **serine protease** family member, mouse **MT-SP1**, that exhibits 86.6% sequence identity. Surface plasmon resonance was used as an independent means of determining the binding constants of the six antibodies. Association rates were as high as 1.15 X 107 s-1 M-1, and dissociation rates were as low as 3.8 X 10-4 s-1. One antibody was shown to detect denatured **MT-SP1** with no cross reactivity to other family members in HeLa or PC3 cells. Another antibody recognized the enzyme in human prostate tissue samples for immunohistochemistry analysis. The mode of binding among the six antibodies and the protease was analyzed by competition ELISA using three distinctly different inhibitors that

mapped the enzyme surface. These antibodies constitute a new class of highly selective protease inhibitors that can be used to dissect the biological roles of proteolytic enzymes as well as to develop diagnostic and therapeutic reagents.
AN 2003:136729 BIOSIS
DN PREV200300136729
TI Potent and selective inhibition of membrane-type **serine protease** 1 by human single-chain antibodies.
AU Sun, Jeonghoon; Pons, Jaume; Craik, Charles S. (1)
CS (1) University of California, San Francisco, 513 Parnassus, Box 0446, San Francisco, CA, 94143-0446, USA: craik@cgl.ucsf.edu USA
SO Biochemistry, (February 4 2003) Vol. 42, No. 4, pp. 892-900. print. ISSN: 0006-2960.
DT Article
LA English

L2 ANSWER 3 OF 42 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AB Matriptase/**MT-SP1** is a novel tumor-associated type II transmembrane **serine protease** that is highly expressed in the epidermis, thymic stroma, and other epithelia. A null mutation was introduced into the Matriptase/**MT-SP1** gene of mice to determine the role of Matriptase/**MT-SP1** in epidermal development and neoplasia. Matriptase/**MT-SP1**-deficient mice developed to term but uniformly died within 48 h of birth. All epidermal surfaces of newborn mice were grossly abnormal with a dry, red, shiny, and wrinkled appearance. Matriptase/**MT-SP1**-deficiency caused striking malformations of the stratum corneum, characterized by dysmorphic and pleomorphic corneocytes and the absence of vesicular bodies in transitional layer cells. This aberrant skin development seriously compromised both inward and outward epidermal barrier function, leading to the rapid and fatal dehydration of Matriptase/**MT-SP1**-deficient pups. Loss of Matriptase/**MT-SP1** also seriously affected hair follicle development resulting in generalized follicular hypoplasia, absence of erupted vibrissae, lack of vibrissal hair canal formation, ingrown vibrissae, and wholesale abortion of vibrissal follicles. Furthermore, Matriptase/**MT-SP1**-deficiency resulted in dramatically increased thymocyte apoptosis, and depletion of thymocytes. This study demonstrates that Matriptase/**MT-SP1** has pleiotropic functions in the development of the epidermis, hair follicles, and cellular immune system.
AN 2002:341644 BIOSIS
DN PREV200200341644
TI Matriptase/**MT-SP1** is required for postnatal survival, epidermal barrier function, hair follicle development, and thymic homeostasis.
AU List, Karin; Haudenschild, Christian C.; Szabo, Roman; Chen, Wanjun; Wahl, Sharon M.; Swaim, William; Engelholm, Lars H.; Behrendt, Niels; Bugge, Thomas H. (1)
CS (1) Proteases and Tissue Remodeling Unit, Oral and Pharyngeal Cancer Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, 30 Convent Drive, Room 211, Bethesda, MD, 20892: thomas.bugge@nih.gov USA
SO Oncogene, (23 May, 2002) Vol. 21, No. 23, pp. 3765-3779. http://www.nature.com/onc. print. ISSN: 0950-9232.
DT Article
LA English

L2 ANSWER 4 OF 42 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AB A cDNA encoding a novel **serine protease**, which we designated spinesin, has been cloned from human spinal cord. The longest open reading frame was 457 amino acids. A homology search revealed that the human spinesin gene was located at chromosome 11q23 and contained 13

exons, the gene structure being similar to that of TMPRSS3 whose gene is also located on 11q23. Spinesin has a simple type II transmembrane structure, consisting of, from the N terminus, a short cytoplasmic domain, a transmembrane domain, a stem region containing a scavenger receptor-like domain, and a **serine protease** domain. Unlike TMPRSS3, it carries no low density lipoprotein receptor domain in the stem region. The extracellular region carries five N-glycosylation sites. The sequence of the protease domain carried the essential triad His, Asp, and Ser and showed some similarity to that of TMPRSS2, hepsin, HAT, **MT-SP1**, TM-PRSS3, and corin, sharing 45.5, 41.9, 41.3, 40.3, 39.1, and 38.5% identity, respectively. The putative mature protease domain preceded by H6DDDDK was produced in Escherichia coli, purified, and successfully activated by immobilized enterokinase. Its optimal pH was about 10. It cleaved synthetic substrates for trypsin, which is inhibited by p-amidinophenylmethanesulfonyl fluoride hydrochloride but not by antipain or leupeptin. Northern blot analysis against mRNA from human tissues including liver, lung, placenta, and heart demonstrated a specific expression of spinesin mRNA in the brain. Immunohistochemically, spinesin was predominantly expressed in neurons, in their axons, and at the synapses of motoneurons in the spinal cord. In addition, some oligodendrocytes were clearly stained. These results indicate that spinesin is transported to the synapses through the axons after its synthesis in the cytoplasm and may play important roles at the synapses. Further analyses are required to clarify its roles at the synapses and in oligodendrocytes.

AN 2002:217589 BIOSIS

DN PREV200200217589

TI Spinesin/TMPRSS5, a novel transmembrane **serine protease**, cloned from human spinal cord.

AU Yamaguchi, Nozomi (1); Okui, Akira; Yamada, Tatsuo; Nakazato, Hiroshi; Mitsui, Shinichi

CS (1) Department of Cell Biology, Research Institute for Neurological Diseases and Geriatrics, Kyoto Prefectural University of Medicine, Kyoto, 602-8566: nozomi@koto.kpu-m.ac.jp Japan

SO Journal of Biological Chemistry, (March 1, 2002) Vol. 277, No. 9, pp. 6806-6812. http://www.jbc.org/. print.
ISSN: 0021-9258.

DT Article

LA English

L2 ANSWER 5 OF 42 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

AB Epithin was originally identified as a mouse type II membrane **serine protease**. Its human orthologue membrane type-**serine protease** 1 (**MT-SP1**)/matriptase has been reported to be localized on the plasma membrane. In addition, soluble forms of matriptase were isolated from human breast milk and breast cancer cell-conditioned medium. In this paper, we report a processing mechanism that appears to be required for the release of epithin. CHO-K1 or COS7 cells transfected with single full-length epithin cDNA generated two different-sized proteins in cell lysates, 110 and 92 kDa. The 92-kDa epithin was found to be an N-terminally truncated form of the 110-kDa epithin, and it was the only form detected in the culture medium. The 92-kDa epithin was also found on the cell surface, where it was anchored by the N-terminal fragment. The results of in vivo cell labeling experiments indicate that the 110-kDa epithin is rapidly processed to the 92-kDa epithin. Using site-directed mutagenesis experiments, we identified Gly149 of the GSVIA sequence in epithin as required for the processing and release of the protein. These results suggest that N-terminal processing of epithin at Gly149 is a necessary prerequisite step for release of the protein.

AN 2002:169451 BIOSIS

DN PREV200200169451

TI N-terminal processing is essential for release of epithin, a mouse type II membrane **serine protease**.

AU Cho, Eun-Gyung; Kim, Moon Gyo; Kim, Chungho; Kim, Seung-Ryul; Seong, Ihn Sik; Chung, Chinha; Schwartz, Ronald H.; Park, Dongeun (1)
CS (1) School of Biological Sciences, Seoul National University, Kwanak-gu, Shilim-dong, Seoul, 151-742: depark@snu.ac.kr South Korea
SO Journal of Biological Chemistry, (November 30, 2001) Vol. 276, No. 48, pp. 44581-44589. http://www.jbc.org/. print.
ISSN: 0021-9258.
DT Article
LA English

L2 ANSWER 6 OF 42 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AB The type II transmembrane multidomain serine proteinase **MT-SP1**/matriptase is highly expressed in many human cancer-derived cell lines and has been implicated in extracellular matrix re-modeling, tumor growth, and metastasis. We have expressed the catalytic domain of **MT-SP1** and solved the crystal structures of complexes with benzamidine at 1.3 ANG and bovine pancreatic trypsin inhibitor at 2.9 ANG. **MT-SP1** exhibits a trypsin-like serine proteinase fold, featuring a unique nine-residue 60-insertion loop that influences interactions with protein substrates. The structure discloses a trypsin-like S1 pocket, a small hydrophobic S2 subsite, and an open negatively charged S4 cavity that favors the binding of basic P3/P4 residues. A complementary charge pattern on the surface opposite the active site cleft suggests a distinct docking of the preceding low density lipoprotein receptor class A domain. The benzamidine crystals possess a freely accessible active site and are hence well suited for soaking small molecules, facilitating the improvement of inhibitors. The crystal structure of the **MT-SP1** complex with bovine pancreatic trypsin inhibitor serves as a model for hepatocyte growth factor activator inhibitor 1, the physiological inhibitor of **MT-SP1**, and suggests determinants for the substrate specificity.
AN 2002:149785 BIOSIS
DN PREV200200149785
TI Catalytic domain structures of **MT-SP1**/matriptase, a matrix-degrading transmembrane serine proteinase.
AU Friedrich, Rainer; Fuentes-Prior, Pablo; Ong, Edgar; Coombs, Gary; Hunter, Michael; Oehler, Ryan; Pierson, Diane; Gonzalez, Richard; Huber, Robert; Bode, Wolfram (1); Madison, Edwin L.
CS (1) Abteilung Strukturforschung, Max-Planck-Institut fuer Biochemie, Am Klopferspitz 18a, 82152, Martinsried: bode@biochem.mpg.de Germany
SO Journal of Biological Chemistry, (January 18, 2002) Vol. 277, No. 3, pp. 2160-2168. http://www.jbc.org/. print.
ISSN: 0021-9258.
DT Article
LA English

L2 ANSWER 7 OF 42 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AB Membrane type-**serine protease** 1 (**MT-SP1**) plays potential roles in the process of invasion and metastasis of carcinomas. In the present study, we cloned a rat **MT-SP1** cDNA and investigated the intestinal distribution and proteolytic properties of the enzyme. By in situ hybridization we found the prominent expression of the mRNA in the epithelial layer of the small intestinal upper villi and of the colon, where cells are loosely attached to the basement membrane. When **MT-SP1** was expressed in Caco-2, a colonic carcinoma cell line, the protein was localized exclusively on the basolateral side. A secreted form of the enzyme produced in COS-1 cells digested fibronectin and laminin. These findings suggest that **MT-SP1** participates in the control of intestinal epithelial turnover by regulating the cell-substratum adhesion.
AN 2001:514690 BIOSIS
DN PREV200100514690
TI A role for membrane-type **serine protease** (**MT-SP1**) in intestinal epithelial turnover.

AU Satomi, Shigeki; Yamasaki, Yoshie; Tsuzuki, Satoshi; Hitomi, Yoshitaka; Iwanaga, Toshihiko; Fushiki, Tohru (1)
CS (1) Laboratory of Nutrition Chemistry, Division of Food Science and Biotechnology, Graduate School of Agriculture, Kyoto University, Kyoto, 606-8502: d53765@sakura.kudpc.kyoto-u.ac.jp Japan
SO Biochemical and Biophysical Research Communications, (October 5, 2001) Vol. 287, No. 4, pp. 995-1002. print.
ISSN: 0006-291X.
DT Article
LA English
SL English

L2 ANSWER 8 OF 42 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AB Membrane-type **serine protease** 1 (**MT-SP1**) was recently cloned, and we now report its biochemical characterization. **MT-SP1** is predicted to be a type II trans-membrane protein with an extracellular protease domain. This localization was experimentally verified using immunofluorescent microscopy and a cell-surface biotinylation technique. The substrate specificity of **MT-SP1** was determined using a positional scanning-synthetic combinatorial library and substrate phage techniques. The preferred cleavage sequences were found to be (P4-(Arg/Lys)P3-(X)P2-(Ser)P1-(Arg)P1'-(Ala)) and (P4-(X)P3-(Arg/Lys)P2-(Ser)P1(Arg) P1'(Ala)), where X is a non-basic amino acid. Protease-activated receptor 2 (PAR2) and single-chain urokinase-type plasminogen activator are proteins that are localized to the extracellular surface and contain the preferred **MT-SP1** cleavage sequence. The ability of **MT-SP1** to activate PARs was assessed by exposing PAR-expressing Xenopus oocytes to the soluble **MT-SP1** protease domain. The latter triggered calcium signaling in PAR2-expressing oocytes at 10 nM but failed to trigger calcium signaling in oocytes expressing PAR1, PAR3, or PAR4 at 100 nM. Single-chain urokinase-type plasminogen activator was activated using catalytic amounts of **MT-SP1** (1 nM), but plasminogen was not cleaved under similar conditions. The membrane localization of **MT-SP1** and its affinity for these key extracellular substrates suggests a role of the proteolytic activity in regulatory events.
AN 2000:452074 BIOSIS
DN PREV200000452074
TI Cellular localization of membrane-type **serine protease** 1 and identification of protease-activated receptor-2 and single-chain urokinase-type plasminogen activator as substrates.
AU Takeuchi, Toshihiko; Harris, Jennifer L.; Huang, Wei; Yan, Kelly W.; Coughlin, Shaun R.; Craik, Charles S. (1)
CS (1) Department of Pharmaceutical Chemistry and Biochemistry and Biophysics, University of California, San Francisco, CA, 94143 USA
SO Journal of Biological Chemistry, (August 25, 2000) Vol. 275, No. 34, pp. 26333-26342. print.
ISSN: 0021-9258.
DT Article
LA English
SL English

L2 ANSWER 9 OF 42 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AB Three novel cDNAs encoding **serine proteases**, that may play a role in early vertebrate development, have been identified from Xenopus laevis. These Xenopus cDNAs encode trypsin-like **serine proteases** and are designated Xenopus embryonic **serine protease** (Xesp)-1, Xesp-2, and XMT-SP1, a homolog of human **MT-SP1**. Xesp-1 is likely to be a secreted protein that functions in the extracellular space. Xesp-2 and XMP-SP1 are likely to be type II membrane proteases with multidomain structures. Xesp-2 has eight low density lipoprotein receptor (LDLR) domains and one scavenger receptor

cysteine-rich (SRCR) domain, and XMT-SP1 has four LDLR domains and two CUB domains. The temporal expressions of these **serine protease** genes show distinct and characteristic patterns during embryogenesis, and they are differently distributed in adult tissues. Overexpression of Xesp-1 caused no significant defect in embryonic development, but overexpression of Xesp-2 or XMT-SP1 caused defective gastrulation or apoptosis, respectively. These results suggest that these proteases may play important roles during early Xenopus development, such as regulation of cell movement in gastrulae.

AN 2000:398381 BIOSIS
DN PREV200000398381
TI Isolation and characterization of three novel **serine protease** genes from Xenopus laevis.
AU Yamada, Kazuto; Takabatake, Takashi; Takeshima, Kazuhito (1)
CS (1) Radioisotope Research Center, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, 464-8602 Japan
SO Gene (Amsterdam), (11 July, 2000) Vol. 252, No. 1-2, pp. 209-216. print. ISSN: 0378-1119.
DT Article
LA English
SL English

L2 ANSWER 10 OF 42 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AB **Serine proteases** of the chymotrypsin fold are of great interest because they provide detailed understanding of their enzymatic properties and their proposed role in a number of physiological and pathological processes. We have been developing the macromolecular inhibitor ecotin to be a "fold-specific" inhibitor that is selective for members of the chymotrypsin-fold class of proteases. Inhibition of protease activity through the use of wild-type and engineered ecotins results in inhibition of rat prostate differentiation and retardation of the growth of human PC-3 prostatic cancer tumors. In an effort to identify the proteases that may be involved in these processes, reverse transcription-PCR with PC-3 poly(A)+ mRNA was performed by using degenerate oligonucleotide primers. These primers were designed by using conserved protein sequences unique to chymotrypsin-fold **serine proteases**. Five proteases were identified: urokinase-type plasminogen activator, factor XII, protein C, trypsinogenIV, and a protease that we refer to as membrane-type **serine protease** 1 (**MT-SP1**). The cloning and characterization of the **MT-SP1** cDNA shows that it encodes a mosaic protein that contains a transmembrane signal anchor, two CUB domains, four LDLR repeats, and a **serine protease** domain. Northern blotting shows broad expression of **MT-SP1** in a variety of epithelial tissues with high levels of expression in the human gastrointestinal tract and the prostate. A His-tagged fusion of the **MT-SP1** protease domain was expressed in Escherichia coli, purified, and autoactivated. Ecotin and variant ecotins are subnanomolar inhibitors of the **MT-SP1** activated protease domain, suggesting a possible role for **MT-SP1** in prostate differentiation and the growth of prostatic carcinomas.

AN 1999:505836 BIOSIS
DN PREV199900505836
TI Reverse biochemistry: Use of macromolecular protease inhibitors to dissect complex biological processes and identify a membrane-type **serine protease** in epithelial cancer and normal tissue.
AU Takeuchi, Toshihiko; Shuman, Marc A.; Craik, Charles S. (1)
CS (1) Departments of Pharmaceutical Chemistry and Biochemistry and Biophysics, University of California, San Francisco, CA, 94143 USA
SO Proceedings of the National Academy of Sciences of the United States of America, (Sept. 28, 1999) Vol. 96, No. 20, pp. 11054-11061. ISSN: 0027-8424.
DT Article

LA English
SL English

L2 ANSWER 11 OF 42 LIFESCI COPYRIGHT 2003 CSA
AB Matriptase/**MT**-**SP1** is a novel tumor-associated type II transmembrane **serine protease** that is highly expressed in the epidermis, thymic stroma, and other epithelia. A null mutation was introduced into the Matriptase/**MT**-**SP1** gene of mice to determine the role of Matriptase/**MT**-**SP1** in epidermal development and neoplasia. Matriptase/**MT**-**SP1**-deficient mice developed to term but uniformly died within 48 h of birth. All epidermal surfaces of newborn mice were grossly abnormal with a dry, red, shiny, and wrinkled appearance. Matriptase/**MT**-**SP1**-deficiency caused striking malformations of the stratum corneum, characterized by dysmorphic and pleomorphic corneocytes and the absence of vesicular bodies in transitional layer cells. This aberrant skin development seriously compromised both inward and outward epidermal barrier function, leading to the rapid and fatal dehydration of Matriptase/**MT**-**SP1**-deficient pups. Loss of Matriptase/**MT**-**SP1** also seriously affected hair follicle development resulting in generalized follicular hypoplasia, absence of erupted vibrissae, lack of vibrissal hair canal formation, ingrown vibrissae, and wholesale abortion of vibrissal follicles. Furthermore, Matriptase/**MT**-**SP1**-deficiency resulted in dramatically increased thymocyte apoptosis, and depletion of thymocytes. This study demonstrates that Matriptase/**MT**-**SP1** has pleiotropic functions in the development of the epidermis, hair follicles, and cellular immune system.
AN 2002:103783 LIFESCI
TI Matriptase/**MT**-**SP1** is required for postnatal survival, epidermal barrier function, hair follicle development, and thymic homeostasis
AU List, K.; Haudenschild, C.C.; Szabo, R.; Chen, W.; Wahl, S.M.; Swaim, W.; Engelholm, L.H.; Behrendt, N.; Bugge, T.H.
CS Proteases and Tissue Remodeling Unit, Oral and Pharyngeal Cancer Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, 30 Convent Drive, Room 211, Bethesda, Maryland, MD 20892, USA; E-mail: thomas.bugge@nih.gov
SO Oncogene, (20020523) vol. 21, no. 23, pp. 3765-3779.
ISSN: 0950-9232.
DT Journal
FS G; B
LA English
SL English

L2 ANSWER 12 OF 42 LIFESCI COPYRIGHT 2003 CSA
AB A cDNA encoding a novel **serine protease**, which we designated spinesin, has been cloned from human spinal cord. The longest open reading frame was 457 amino acids. A homology search revealed that the human spinesin gene was located at chromosome 11q23 and contained 13 exons, the gene structure being similar to that of TMPRSS3 whose gene is also located on 11q23. Spinesin has a simple type II transmembrane structure, consisting of, from the N terminus, a short cytoplasmic domain, a transmembrane domain, a stem region containing a scavenger receptor-like domain, and a **serine protease** domain. Unlike TMPRSS3, it carries no low density lipoprotein receptor domain in the stem region. The extracellular region carries five N-glycosylation sites. The sequence of the protease domain carried the essential triad His, Asp, and Ser and showed some similarity to that of TMPRSS2, hepsin, HAT, **MT**-**SP1**, TMPRSS3, and corin, sharing 45.5, 41.9, 41.3, 40.3, 39.1, and 38.5% identity, respectively. The putative mature protease domain preceded by H sub(6)DDDDK was produced in Escherichia coli, purified, and successfully activated by immobilized enterokinase. Its optimal pH was about 10. It cleaved synthetic substrates for trypsin, which is inhibited

by p-amidinophenylmethanesulfonyl fluoride hydrochloride but not by antipain or leupeptin. Northern blot analysis against mRNA from human tissues including liver, lung, placenta, and heart demonstrated a specific expression of spinesin mRNA in the brain. Immunohistochemically, spinesin was predominantly expressed in neurons, in their axons, and at the synapses of motoneurons in the spinal cord. In addition, some oligodendrocytes were clearly stained. These results indicate that spinesin is transported to the synapses through the axons after its synthesis in the cytoplasm and may play important roles at the synapses. Further analyses are required to clarify its roles at the synapses and in oligodendrocytes.

AN 2002:38920 LIFESCI
TI Spinesin/TMPRSS5, a Novel Transmembrane **Serine Protease** , Cloned from Human Spinal Cord
AU Yamaguchi, N.; Okui, A.; Yamada, T.; Nakazato, H.; Mitsui, S.
CS Department of Cell Biology, Research, Kyoto Prefectural University of Medicine, Kyoto 602-8566, Japan; E-mail: nozomi@koto.kpu-m.ac.jp
SO Journal of Biological Chemistry [J. Biol. Chem.], (20020301) vol. 277, no. 9, pp. 6806-6812.
ISSN: 0021-9258.
DT Journal
FS N
LA English
SL English

L2 ANSWER 13 OF 42 LIFESCI COPYRIGHT 2003 CSA
AB Epithin was originally identified as a mouse type II membrane **serine protease**. Its human orthologue membrane type-**serine protease** 1 (**MT-SP1**)/matriptase has been reported to be localized on the plasma membrane. In addition, soluble forms of matriptase were isolated from human breast milk and breast cancer cell-conditioned medium. In this paper, we report a processing mechanism that appears to be required for the release of epithin. CHO-K1 or COS7 cells transfected with single full-length epithin cDNA generated two different-sized proteins in cell lysates, 110 and 92 kDa. The 92-kDa epithin was found to be an N-terminally truncated form of the 110-kDa epithin, and it was the only form detected in the culture medium. The 92-kDa epithin was also found on the cell surface, where it was anchored by the N-terminal fragment. The results of in vivo cell labeling experiments indicate that the 110-kDa epithin is rapidly processed to the 92-kDa epithin. Using site-directed mutagenesis experiments, we identified Gly super(149) of the GSVIA sequence in epithin as required for the processing and release of the protein. These results suggest that N-terminal processing of epithin at Gly super(149) is a necessary prerequisite step for release of the protein.

AN 2002:7963 LIFESCI
TI N-terminal Processing Is Essential for Release of Epithin, a Mouse Type II Membrane **Serine Protease**
AU Cho, E.; Kim, M.G.; Kim, C.; Kim, S.; Seong, I.S.; Chung, C.; Schwartz, R.H.; Park, D.
CS School of Biological Sciences, Seoul National University, Seoul 151-742, Republic of Korea; E-mail: depark@snu.ac.kr
SO Journal of Biological Chemistry [J. Biol. Chem.], (20011130) vol. 276, no. 48, pp. 44581-44589.
ISSN: 0021-9258.
DT Journal
FS N
LA English
SL English

L2 ANSWER 14 OF 42 LIFESCI COPYRIGHT 2003 CSA
AB Membrane type-**serine protease** 1 (**MT-SP1**) plays potential roles in the process of invasion and metastasis of carcinomas. In the present study, we cloned a rat **MT**

-**SP1** cDNA and investigated the intestinal distribution and proteolytic properties of the enzyme. By in situ hybridization we found the prominent expression of the mRNA in the epithelial layer of the small intestinal upper villi and of the colon, where cells are loosely attached to the basement membrane. When **MT-SP1** was expressed in Caco-2, a colonic carcinoma cell line, the protein was localized exclusively on the basolateral side. A secreted form of the enzyme produced in COS-1 cells digested fibronectin and laminin. These findings suggest that **MT-SP1** participates in the control of intestinal epithelial turnover by regulating the cell-substratum adhesion. Copyright 2001 Academic Press.

AN 2001:107283 LIFESCI
TI A Role for Membrane-Type **Serine Protease** (**MT-SP1**) in Intestinal Epithelial Turnover
AU Satomi, S.; Yamasaki, Y.; Tsuzuki, S.; Hitomi, Y.; Iwanaga, T.; Fushiki, T.*
CS Laboratory of Nutrition Chemistry, Division of Food Science and Biotechnology, Graduate School of Agriculture, Kyoto University, Kyoto, 606-8502, Japan; E-mail: d53765@sakura.kudpc.kyoto-u.ac.jp
SO Biochemical and Biophysical Research Communications [Biochem. Biophys. Res. Commun.], (20011005) vol. 287, no. 4, pp. 995-1002. ISSN: 0006-291X.
DT Journal
FS N; G
LA English
SL English

L2 ANSWER 15 OF 42 LIFESCI COPYRIGHT 2003 CSA
AB Three novel cDNAs encoding **serine proteases**, that may play a role in early vertebrate development, have been identified from Xenopus laevis. These Xenopus cDNAs encode trypsin-like **serine proteases** and are designated Xenopus embryonic **serine protease** (Xesp)-1, Xesp-2, and XMT-SP1, a homolog of human **MT-SP1**. Xesp-1 is likely to be a secreted protein that functions in the extracellular space. Xesp-2 and XMP-SP1 are likely to be type II membrane proteases with multidomain structures. Xesp-2 has eight low density lipoprotein receptor (LDLR) domains and one scavenger receptor cysteine-rich (SRCR) domain, and XMT-SP1 has four LDLR domains and two CUB domains. The temporal expressions of these **serine protease** genes show distinct and characteristic patterns during embryogenesis, and they are differently distributed in adult tissues. Overexpression of Xesp-1 caused no significant defect in embryonic development, but overexpression of Xesp-2 or XMT-SP1 caused defective gastrulation or apoptosis, respectively. These results suggest that these proteases may play important roles during early Xenopus development, such as regulation of cell movement in gastrulae.

AN 2001:2396 LIFESCI
TI Isolation and characterization of three novel **serine protease** genes from Xenopus laevis
AU Yamada, K.; Takabatake, T.; Takeshima, K.*
CS Graduate School of Human Informatics, Nagoya University, Furo-cho, Chikusa-ku, 464-8601 Nagoya Japan
SO Gene, (20000711) vol. 252, no. 1-2, pp. 209-216. ISSN: 0378-1119.
DT Journal
FS N; G
LA English
SL English

L2 ANSWER 16 OF 42 USPATFULL
AB Provided herein is are polypeptides that include the protease domain of a type II transmembrane **serine protease** (MTSP) as a single chain. Methods using the polypeptides to identify compounds that modulate the protease activity of an MTSP are provided. Also provided

are MTSPs designated MTSP3 and MTSP4 and a form of an MTSP designated MTSP6.

AN 2003:173324 USPATFULL

TI Nucleic acid molecules encoding transmembrane **serine proteases**, the encoded proteins and methods based thereon

IN Madison, Edwin L., San Diego, CA, UNITED STATES
Ong, Edgar O., San Diego, CA, UNITED STATES
Yeh, Jiunn-Chern, San Diego, CA, UNITED STATES

PA Corvas International, Inc. (U.S. corporation)

PI US 2003119168 A1 20030626

AI US 2001-776191 A1 20010202 (9)

RLI Continuation-in-part of Ser. No. US 2000-657986, filed on 8 Sep 2000, PENDING

PRAI US 2000-179982P 20000203 (60)
US 2000-183542P 20000218 (60)
US 2000-213124P 20000622 (60)
US 2000-220970P 20000726 (60)
US 2000-234840P 20000922 (60)

DT Utility

FS APPLICATION

LREP ELLER EHRMAN WHITE & MCAULIFFE LLP, 4350 LA JOLLA VILLAGE DRIVE, 7TH FLOOR, SAN DIEGO, CA, 92122-1246

CLMN Number of Claims: 136

ECL Exemplary Claim: 1

DRWN 8 Drawing Page(s)

LN.CNT 9872

L2 ANSWER 17 OF 42 USPATFULL

AB Isolated Dendritic Cell Transmembrane **Serine Proteases**, DNAs encoding such **serine proteases**, and pharmaceutical and/or diagnostic compositions made therefrom, are disclosed. The isolated **serine proteases** can be used to hydrolyze peptide bonds. The **serine proteases** are also useful in screening for inhibitors or agonists thereof.

AN 2003:120302 USPATFULL

TI Dendritic cell transmembrane **serine protease**

IN Anderson, Dirk M., Seattle, WA, UNITED STATES
Virca, G. Duke, Bellevue, WA, UNITED STATES

PI US 2003082783 A1 20030501

AI US 2002-177661 A1 20020620 (10)

PRAI US 2001-299606P 20010620 (60)

DT Utility

FS APPLICATION

LREP Immunex Corporation, Law Department, 51 University Street, Seattle, WA, 98101

CLMN Number of Claims: 19

ECL Exemplary Claim: 1

DRWN 1 Drawing Page(s)

LN.CNT 2428

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 18 OF 42 USPATFULL

AB The present invention provides compounds which inhibit **serine protease** activity of matriptase or MTSP1. Also provided are pharmaceutical compositions comprising those compounds and methods of using the compounds and pharmaceutical compositions to treat conditions ameliorated by inhibition of matriptase or MTSP1.

AN 2003:71964 USPATFULL

TI Inhibitors of **serine protease** activity of matriptase or MTSP1

IN Semple, Joseph E., San Diego, CA, UNITED STATES
Coombs, Gary S., San Diego, CA, UNITED STATES
Reiner, John E., San Diego, CA, UNITED STATES
Ong, Edgar O., San Diego, CA, UNITED STATES

Araldi, Gian Luca, Plymouth, MA, UNITED STATES
PI US 2003050251 A1 20030313
AI US 2002-92004 A1 20020305 (10)
RLI Continuation-in-part of Ser. No. WO 2001-US28137, filed on 7 Sep 2001, PENDING Continuation-in-part of Ser. No. US 2000-657986, filed on 8 Sep 2000, PENDING
DT Utility
FS APPLICATION
LREP Pillsbury Winthrop LLP, Intellectual Property Group, Suite 200, 11682 El Camino Real, San Diego, CA, 92130
CLMN Number of Claims: 36
ECL Exemplary Claim: 1
DRWN 12 Drawing Page(s)
LN.CNT 1982
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 19 OF 42 USPATFULL
AB The present invention relates to the compositions, methods, and applications of a new approach to pattern recognition based targeting by which an exponential amplification of effector response can be specifically obtained at a targeted cells. The purpose of this invention is to enable the selective delivery of large quantities of an array of effector molecules to target cells for diagnostic or therapeutic purposes. The invention is comprised of two components designated as "Compound 1" and "Compound 2": Compound 1 is comprised of a cell binding agent and a masked female adaptor. Compound 2 is comprised of a male ligand, an effector agent, and two or more masked female receptors. The male ligand is selected to bind with high affinity to the female adaptor. Compound 1 can bind with high affinity to the target cell and the female receptor can then be unmasked by an enzyme enriched at the tumor cell. The male ligand of Compound 2 can then bind to the unmasked female adaptor bound to the target cell. The masked female adaptor on the bound Compound 2 can then be specifically unmasked. One receptor has in effect become two. Two new molecules of Compound 2 can bind to the unmasked adaptors receptors. After unmasking two receptors in effect become four. The process can continue in an explosive exponential like fashion resulting in enormous amplification of the number of effector molecules specifically deposited at the target cell.
AN 2003:44367 USPATFULL
TI Exponential pattern recognition based cellular targeting, compositions, methods and anticancer applications
IN Glazier, Arnold, Newton, MA, UNITED STATES
PA Drug Innovation & Design, Incorporated, Waltham, MA (U.S. corporation)
PI US 2003031677 A1 20030213
AI US 2002-179610 A1 20020624 (10)
PRAI US 2001-300805P 20010625 (60)
DT Utility
FS APPLICATION
LREP HAMILTON, BROOK, SMITH & REYNOLDS, P.C., 530 VIRGINIA ROAD, P.O. BOX 9133, CONCORD, MA, 01742-9133
CLMN Number of Claims: 43
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 3103
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 20 OF 42 MEDLINE
AB Membrane type **serine protease** 1 (**MT-SP1**) is a representative member of a large family of related enzymes known as type II transmembrane **serine proteases** or membrane type **serine proteases**. **MT-SP1** has been implicated in the selective proteolysis of key extracellular substrates but its physiological role is still not fully understood. **MT-SP1** expression at the protein and RNA

level has been previously examined by nonquantitative methods such as in situ hybridization, Northern blotting and immunohistochemistry. To establish an introductory understanding of the quantitative mRNA expression of **MT-SP1** and to correlate these levels with urokinase-type plasminogen activator receptor (uPAR), a key component of extracellular proteolysis, quantitative RT-PCR was carried out. RNA expression was analyzed in 34 human cancer cell lines, 26 human tissues and 18 primary human breast cancer tissue samples. **MT-SP1** mRNA is highly expressed in many breast, ovarian, prostate and colon cancer cell lines and normal human tissues of endodermal origin. At the transcript level, **MT-SP1** shows a highly statistically significant correlation (Pearson's product moment correlation r = 0.784, p < 0.001) with uPAR in human breast cancer tissue. The exact role of **MT-SP1** in concert with proteins such as uPAR and other members of the plasminogen activator cascade has yet to be ascertained. However, the significant correlation between **MT-SP1** and uPAR transcript levels in this initial study suggests further work to establish the role of **MT-SP1** as a possible prognostic, diagnostic or therapeutic target for breast cancer.

AN 2003158495 IN-PROCESS
DN 22561865 PubMed ID: 12675519
TI Quantitation of membrane type **serine protease** 1 (**MT-SP1**) in transformed and normal cells.
AU Bhatt Ami S; Takeuchi Toshi; Ylstra Bauke; Ginzinger David; Albertson Donna; Shuman Marc A; Craik Charles S
CS University of California at San Francisco, School of Medicine, 513 Parnassus Ave, Box 0454, San Francisco, CA 94143, USA.
NC CA 72006 (NCI)
GM07618 (NIGMS)
SO BIOLOGICAL CHEMISTRY, (2003 Feb) 384 (2) 257-66.
Journal code: 9700112. ISSN: 1431-6730.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20030406
Last Updated on STN: 20030406

L2 ANSWER 21 OF 42 MEDLINE
AB Many **serine proteases** play important regulatory roles in complex biological systems, but only a few have been linked directly with capillary morphogenesis and angiogenesis. Here we provide evidence that **serine protease** activities, independent of the plasminogen activation cascade, are required for microvascular endothelial cell reorganization and capillary morphogenesis in vitro. A homology cloning approach targeting conserved motifs present in all **serine proteases**, was used to identify candidate **serine proteases** involved in these processes, and revealed 5 genes (acrosin, testisin, neurosin, PSP and neurotrypsin), none of which had been associated previously with expression in endothelial cells. A subsequent gene-specific RT-PCR screen for 22 **serine proteases** confirmed expression of these 5 genes and identified 7 additional **serine protease** genes expressed by human endothelial cells, urokinase-type plasminogen activator, protein C, TMPRSS2, hepsin, matriptase/**MT-SP1**, dipeptidylpeptidase IV, and seprase. Differences in **serine protease** gene expression between microvascular and human umbilical vein endothelial cells (HUVECs) were identified and several **serine protease** genes were found to be regulated by the nature of the substratum, ie. artificial basement membrane or fibrillar type I collagen. mRNA transcripts of several **serine protease** genes were associated with blood vessels in vivo by in situ hybridization of human tissue specimens. These data suggest a potential role for **serine proteases**, not previously associated with endothelium, in vascular

function and angiogenesis.
AN 2003111572 IN-PROCESS
DN 22512033 PubMed ID: 12624642
TI Endothelial cell **serine proteases** expressed during vascular morphogenesis and angiogenesis.
AU Aimes Ronald T; Zijlstra Andries; Hooper John D; Ogbourne Steven M; Sit Mae-Le; Fuchs Simone; Gotley David C; Quigley James P; Antalis Toni M
CS Department of Vascular Biology, Holland Laboratory, American Red Cross, 15601 Crabbs Branch Way, Rockville, MD 20855, USA.
SO THROMBOSIS AND HAEMOSTASIS, (2003 Mar) 89 (3) 561-72.
Journal code: 7608063. ISSN: 0340-6245.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20030308
Last Updated on STN: 20030308

L2 ANSWER 22 OF 42 MEDLINE
AB Specific human antibodies targeting proteases expressed on cancer cells can be valuable reagents for diagnosis, prognosis, and therapy of cancer. To this end, a phage-displayed antibody library was screened against a cancer-associated **serine protease**, **MT-SP1**. A protein inhibitor of **serine proteases** that binds to a defined surface of **MT-SP1** was used in an affinity-based washing procedure. Six antibodies were selected on the basis of their ELISA profiles and ability to serve as useful immunological reagents. The apparent K(i), indicative of the potency of the antibodies at inhibiting human **MT-SP1** activity, ranged from 50 pM to 129 nM. Two of the antibodies had approximately 800-fold and 1500-fold selectivity when tested against the most homologous **serine protease** family member, mouse **MT-SP1**, that exhibits 86.6% sequence identity. Surface plasmon resonance was used as an independent means of determining the binding constants of the six antibodies. Association rates were as high as 1.15 x 10(7) s(-)(1) M(-)(1), and dissociation rates were as low as 3.8 x 10(-)(4) s(-)(1). One antibody was shown to detect denatured **MT-SP1** with no cross reactivity to other family members in HeLa or PC3 cells. Another antibody recognized the enzyme in human prostate tissue samples for immunohistochemistry analysis. The mode of binding among the six antibodies and the protease was analyzed by competition ELISA using three distinctly different inhibitors that mapped the enzyme surface. These antibodies constitute a new class of highly selective protease inhibitors that can be used to dissect the biological roles of proteolytic enzymes as well as to develop diagnostic and therapeutic reagents.
AN 2003042346 MEDLINE
DN 22438695 PubMed ID: 12549907
TI Potent and selective inhibition of membrane-type **serine protease** 1 by human single-chain antibodies.
AU Sun Jeonghoon; Pons Jaume; Craik Charles S
CS Department of Pharmaceutical Chemistry, University of California, San Francisco, 513 Parnassus, San Francisco, California 94143, USA.
NC CA72006 (NCI)
SO BIOCHEMISTRY, (2003 Feb 4) 42 (4) 892-900.
Journal code: 0370623. ISSN: 0006-2960.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200303
ED Entered STN: 20030129
Last Updated on STN: 20030328
Entered Medline: 20030327

L2 ANSWER 23 OF 42 MEDLINE
AB Matriptase/**MT-SP1** is a novel tumor-associated type II transmembrane **serine protease** that is highly expressed in the epidermis, thymic stroma, and other epithelia. A null mutation was introduced into the Matriptase/**MT-SP1** gene of mice to determine the role of Matriptase/**MT-SP1** in epidermal development and neoplasia. Matriptase/**MT-SP1**-deficient mice developed to term but uniformly died within 48 h of birth. All epidermal surfaces of newborn mice were grossly abnormal with a dry, red, shiny, and wrinkled appearance. Matriptase/**MT-SP1**-deficiency caused striking malformations of the stratum corneum, characterized by dysmorphic and pleomorphic corneocytes and the absence of vesicular bodies in transitional layer cells. This aberrant skin development seriously compromised both inward and outward epidermal barrier function, leading to the rapid and fatal dehydration of Matriptase/**MT-SP1**-deficient pups. Loss of Matriptase/**MT-SP1** also seriously affected hair follicle development resulting in generalized follicular hypoplasia, absence of erupted vibrissae, lack of vibrissal hair canal formation, ingrown vibrissae, and wholesale abortion of vibrissal follicles. Furthermore, Matriptase/**MT-SP1**-deficiency resulted in dramatically increased thymocyte apoptosis, and depletion of thymocytes. This study demonstrates that Matriptase/**MT-SP1** has pleiotropic functions in the development of the epidermis, hair follicles, and cellular immune system.
AN 2002290948 MEDLINE
DN 22028791 PubMed ID: 12032844
TI Matriptase/**MT-SP1** is required for postnatal survival, epidermal barrier function, hair follicle development, and thymic homeostasis.
AU List Karin; Haudenschild Christian C; Szabo Roman; Chen WanJun; Wahl Sharon M; Swaim William; Engelholm Lars H; Behrendt Niels; Bugge Thomas H
CS Oral and Pharyngeal Cancer Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, 30 Convent Drive, Bethesda, Maryland, MD 20892, USA.
SO ONCOGENE, (2002 May 23) 21 (23) 3765-79.
Journal code: 8711562. ISSN: 0950-9232.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200206
ED Entered STN: 20020529
Last Updated on STN: 20020615
Entered Medline: 20020614

L2 ANSWER 24 OF 42 MEDLINE
AB A cDNA encoding a novel **serine protease**, which we designated spinesin, has been cloned from human spinal cord. The longest open reading frame was 457 amino acids. A homology search revealed that the human spinesin gene was located at chromosome 11q23 and contained 13 exons, the gene structure being similar to that of TMPRSS3 whose gene is also located on 11q23. Spinesin has a simple type II transmembrane structure, consisting of, from the N terminus, a short cytoplasmic domain, a transmembrane domain, a stem region containing a scavenger receptor-like domain, and a **serine protease** domain. Unlike TMPRSS3, it carries no low density lipoprotein receptor domain in the stem region. The extracellular region carries five N-glycosylation sites. The sequence of the protease domain carried the essential triad His, Asp, and Ser and showed some similarity to that of TMPRSS2, hepsin, HAT, **MT-SP1**, TMPRSS3, and corin, sharing 45.5, 41.9, 41.3, 40.3, 39.1, and 38.5% identity, respectively. The putative mature protease domain preceded by H(6)DDDDK was produced in Escherichia coli, purified, and successfully activated by immobilized enterokinase. Its optimal pH was

about 10. It cleaved synthetic substrates for trypsin, which is inhibited by p-amidinophenylmethanesulfonyl fluoride hydrochloride but not by antipain or leupeptin. Northern blot analysis against mRNA from human tissues including liver, lung, placenta, and heart demonstrated a specific expression of spinesin mRNA in the brain. Immunohistochemically, spinesin was predominantly expressed in neurons, in their axons, and at the synapses of motoneurons in the spinal cord. In addition, some oligodendrocytes were clearly stained. These results indicate that spinesin is transported to the synapses through the axons after its synthesis in the cytoplasm and may play important roles at the synapses. Further analyses are required to clarify its roles at the synapses and in oligodendrocytes.

AN 2002142261 MEDLINE
DN 21850647 PubMed ID: 11741986
TI Spinesin/TMPRSS5, a novel transmembrane **serine protease** , cloned from human spinal cord.
AU Yamaguchi Nozomi; Okui Akira; Yamada Tatsuo; Nakazato Hiroshi; Mitsui Shinichi
CS Department of Cell Biology, Research Institute for Neurological Diseases and Geriatrics, Kyoto Prefectural University of Medicine, Kyoto 602-8566, Japan.. nozomi@koto.kpu-m.ac.jp
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Mar 1) 277 (9) 6806-12. Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-AB028140
EM 200204
ED Entered STN: 20020307
Last Updated on STN: 20030105
Entered Medline: 20020401

L2 ANSWER 25 OF 42 MEDLINE
AB Epithin was originally identified as a mouse type II membrane **serine protease**. Its human orthologue membrane type-**serine protease** 1 (**MT-SP1**)/matriptase has been reported to be localized on the plasma membrane. In addition, soluble forms of matriptase were isolated from human breast milk and breast cancer cell-conditioned medium. In this paper, we report a processing mechanism that appears to be required for the release of epithin. CHO-K1 or COS7 cells transfected with single full-length epithin cDNA generated two different-sized proteins in cell lysates, 110 and 92 kDa. The 92-kDa epithin was found to be an N-terminally truncated form of the 110-kDa epithin, and it was the only form detected in the culture medium. The 92-kDa epithin was also found on the cell surface, where it was anchored by the N-terminal fragment. The results of in vivo cell labeling experiments indicate that the 110-kDa epithin is rapidly processed to the 92-kDa epithin. Using site-directed mutagenesis experiments, we identified Gly(149) of the GSVIA sequence in epithin as required for the processing and release of the protein. These results suggest that N-terminal processing of epithin at Gly(149) is a necessary prerequisite step for release of the protein.
AN 2001687698 MEDLINE
DN 21576175 PubMed ID: 11567025
TI N-terminal processing is essential for release of epithin, a mouse type II membrane **serine protease**.
AU Cho E G; Kim M G; Kim C; Kim S R; Seong I S; Chung C; Schwartz R H; Park D
CS School of Biological Sciences, Seoul National University, Seoul 151-742, Republic of Korea.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Nov 30) 276 (48) 44581-9. Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Priority Journals
EM 200201
ED Entered STN: 20011206
Last Updated on STN: 20030105
Entered Medline: 20020110

L2 ANSWER 26 OF 42 MEDLINE
AB Membrane type-**serine protease** 1 (**MT-SP1**) plays potential roles in the process of invasion and metastasis of carcinomas. In the present study, we cloned a rat **MT-SP1** cDNA and investigated the intestinal distribution and proteolytic properties of the enzyme. By in situ hybridization we found the prominent expression of the mRNA in the epithelial layer of the small intestinal upper villi and of the colon, where cells are loosely attached to the basement membrane. When **MT-SP1** was expressed in Caco-2, a colonic carcinoma cell line, the protein was localized exclusively on the basolateral side. A secreted form of the enzyme produced in COS-1 cells digested fibronectin and laminin. These findings suggest that **MT-SP1** participates in the control of intestinal epithelial turnover by regulating the cell-substratum adhesion.
Copyright 2001 Academic Press.
AN 2001528039 MEDLINE
DN 21458307 PubMed ID: 11573963
TI A role for membrane-type **serine protease** (**MT-SP1**) in intestinal epithelial turnover.
AU Satomi S; Yamasaki Y; Tsuzuki S; Hitomi Y; Iwanaga T; Fushiki T
CS Laboratory of Nutrition Chemistry, Division of Food Science and Biotechnology, Graduate School of Agriculture, Kyoto University, Kyoto 606-8502, Japan.
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2001 Oct 5) 287 (4) 995-1002.
Journal code: 0372516. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-AB037898
EM 200112
ED Entered STN: 20011001
Last Updated on STN: 20020122
Entered Medline: 20011204

L2 ANSWER 27 OF 42 MEDLINE
AB Membrane-type **serine protease** 1 (**MT-SP1**) was recently cloned, and we now report its biochemical characterization. **MT-SP1** is predicted to be a type II transmembrane protein with an extracellular protease domain. This localization was experimentally verified using immunofluorescent microscopy and a cell-surface biotinylation technique. The substrate specificity of **MT-SP1** was determined using a positional scanning-synthetic combinatorial library and substrate phage techniques. The preferred cleavage sequences were found to be (P4-(Arg/Lys)P3-(X)P2-(Ser)P1-(Arg)P1'-(Ala)) and (P4-(X)P3-(Arg/Lys)P2-(Ser)P1(Arg) P1'(Ala)), where X is a non-basic amino acid. Protease-activated receptor 2 (PAR2) and single-chain urokinase-type plasminogen activator are proteins that are localized to the extracellular surface and contain the preferred **MT-SP1** cleavage sequence. The ability of **MT-SP1** to activate PARs was assessed by exposing PAR-expressing Xenopus oocytes to the soluble **MT-SP1** protease domain. The latter triggered calcium signaling in PAR2-expressing oocytes at 10 nm but failed to trigger calcium signaling in oocytes expressing PAR1, PAR3, or PAR4 at 100 nm.

Single-chain urokinase-type plasminogen activator was activated using catalytic amounts of **MT-SP1** (1 nm), but plasminogen was not cleaved under similar conditions. The membrane localization of **MT-SP1** and its affinity for these key extracellular substrates suggests a role of the proteolytic activity in regulatory events.

AN 2000458591 MEDLINE
DN 20408983 PubMed ID: 10831593
TI Cellular localization of membrane-type **serine protease** 1 and identification of protease-activated receptor-2 and single-chain urokinase-type plasminogen activator as substrates.
AU Takeuchi T; Harris J L; Huang W; Yan K W; Coughlin S R; Craik C S
CS Department of Pharmaceutical Chemistry and Biochemistry and Biophysics, Cardiovascular Research Institute, University of California, San Francisco, California 94143, USA.
NC CA71097 (NCI)
CA72006 (NCI)
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Aug 25) 275 (34) 26333-42.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200009
ED Entered STN: 20001005
Last Updated on STN: 20001005
Entered Medline: 20000925

L2 ANSWER 28 OF 42 MEDLINE
AB Three novel cDNAs encoding **serine proteases**, that may play a role in early vertebrate development, have been identified from Xenopus laevis. These Xenopus cDNAs encode trypsin-like **serine proteases** and are designated Xenopus embryonic **serine protease** (Xesp)-1, Xesp-2, and XMT-SP1, a homolog of human **MT-SP1**. Xesp-1 is likely to be a secreted protein that functions in the extracellular space. Xesp-2 and XMP-SP1 are likely to be type II membrane proteases with multidomain structures. Xesp-2 has eight low density lipoprotein receptor (LDLR) domains and one scavenger receptor cysteine-rich (SRCR) domain, and XMT-SP1 has four LDLR domains and two CUB domains. The temporal expressions of these **serine protease** genes show distinct and characteristic patterns during embryogenesis, and they are differently distributed in adult tissues. Overexpression of Xesp-1 caused no significant defect in embryonic development, but overexpression of Xesp-2 or XMT-SP1 caused defective gastrulation or apoptosis, respectively. These results suggest that these proteases may play important roles during early Xenopus development, such as regulation of cell movement in gastrulae.
AN 2000457900 MEDLINE
DN 20363741 PubMed ID: 10903452
TI Isolation and characterization of three novel **serine protease** genes from Xenopus laevis.
AU Yamada K; Takabatake T; Takeshima K
CS Graduate School of Human Informatics, Nagoya University, Furo-cho, Chikusa-ku, 464-8601, Nagoya, Japan.
SO GENE, (2000 Jul 11) 252 (1-2) 209-16.
Journal code: 7706761. ISSN: 0378-1119.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-AB038496; GENBANK-AB038497; GENBANK-AB038498
EM 200009
ED Entered STN: 20001005
Last Updated on STN: 20001005

Entered Medline: 20000925

L2 ANSWER 29 OF 42 MEDLINE
AB **Serine proteases** of the chymotrypsin fold are of great interest because they provide detailed understanding of their enzymatic properties and their proposed role in a number of physiological and pathological processes. We have been developing the macromolecular inhibitor ecotin to be a "fold-specific" inhibitor that is selective for members of the chymotrypsin-fold class of proteases. Inhibition of protease activity through the use of wild-type and engineered ecotins results in inhibition of rat prostate differentiation and retardation of the growth of human PC-3 prostatic cancer tumors. In an effort to identify the proteases that may be involved in these processes, reverse transcription-PCR with PC-3 poly(A)+ mRNA was performed by using degenerate oligonucleotide primers. These primers were designed by using conserved protein sequences unique to chymotrypsin-fold **serine proteases**. Five proteases were identified: urokinase-type plasminogen activator, factor XII, protein C, trypsinogen IV, and a protease that we refer to as membrane-type **serine protease** 1 (**MT-SP1**). The cloning and characterization of the **MT-SP1** cDNA shows that it encodes a mosaic protein that contains a transmembrane signal anchor, two CUB domains, four LDLR repeats, and a **serine protease** domain. Northern blotting shows broad expression of **MT-SP1** in a variety of epithelial tissues with high levels of expression in the human gastrointestinal tract and the prostate. A His-tagged fusion of the **MT-SP1** protease domain was expressed in Escherichia coli, purified, and autoactivated. Ecotin and variant ecotins are subnanomolar inhibitors of the **MT-SP1** activated protease domain, suggesting a possible role for **MT-SP1** in prostate differentiation and the growth of prostatic carcinomas.
AN 1999432178 MEDLINE
DN 99432178 PubMed ID: 10500122
TI Reverse biochemistry: use of macromolecular protease inhibitors to dissect complex biological processes and identify a membrane-type **serine protease** in epithelial cancer and normal tissue.
AU Takeuchi T; Shuman M A; Craik C S
CS Department of Pharmaceutical Chemistry, University of California, San Francisco, CA 94143, USA.
NC CA71097 (NCI)
CA72006 (NCI)
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Sep 28) 96 (20) 11054-61.
Journal code: 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-AF133086
EM 199910
ED Entered STN: 19991101
Last Updated on STN: 20000303
Entered Medline: 19991021

L2 ANSWER 30 OF 42 CAPLUS COPYRIGHT 2003 ACS
AB Membrane-type **serine protease** 1 (**MT-SP1**), identical to matriptase, is a recently identified type II transmembrane **serine protease**. **MT-SP1**/matriptase is of considerable interest for the development, homeostasis, and cancer invasion and metastasis of epithelial tissues. The administration of inhibitors for **MT-SP1**/matriptase may be effective to suppress the development of tumors where the enzyme may be involved. In the present study, we produced a secreted form of

recombinant **MT-SP1**/matriptase (ekMT-SP1s) that can be activated by enterokinase in vitro and investigated the inhibitory ability of various protease inhibitors toward the recombinant enzyme. The enterokinase-treated ekMT-SP1s (active ekMT-SP1s) cleaved various peptidyl-4-methylcoumaryl-7-amide (MCA) substrates with arginine (or lysine) residue at position P1, and the best substrate was t-butyloxycarbonyl (Boc)-Gln-Ala-Arg-MCA. The specificity for the synthetic and natural substrates of the active ekMT-SP1s was in good agreement with that of the natural enzyme. Endogenous protease inhibitors tested, except for antithrombin III, showed no or little inhibition on the cleavage of Boc-Gln-Ala-Arg-MCA by the active ekMT-SP1s. Aprotinin showed strong inhibitory activity toward the cleavage. Food-derived inhibitors, such as soybean trypsin inhibitor, Bowman-Birk inhibitor, and lima bean trypsin inhibitor inhibited it, while chicken ovomucoid did not. Synthetic inhibitors tested inhibited it, and among them, the inhibitory effect of FOY-305 was strongest. The present findings provide important information for the suppression of cancer invasion and metastasis for which **MT-SP1**/matriptase is responsible.

AN 2003:375003 CAPLUS

TI Inhibition of membrane-type **serine protease** 1/matriptase by natural and synthetic protease inhibitors

AU Yamasaki, Yoshie; Satomi, Shigeki; Murai, Nobuhito; Tsuzuki, Satoshi; Fushiki, Tohru

CS Laboratory of Nutrition Chemistry, Division of Food Science and Biotechnology, Graduate School of Agriculture, Kyoto University, Kyoto, 606-8502, Japan

SO Journal of Nutritional Science and Vitaminology (2003), 49(1), 27-32
CODEN: JNSVA5; ISSN: 0301-4800

PB Center for Academic Publications Japan

DT Journal

LA English

RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 31 OF 42 CAPLUS COPYRIGHT 2003 ACS

AB Membrane type **serine protease** 1 (**MT-SP1**) is a representative member of a large family of related enzymes known as type II transmembrane **serine proteases** or membrane type **serine proteases**. **MT-SP1** has been implicated in the selective proteolysis of key extracellular substrates but its physiol. role is still not fully understood. **MT-SP1** expression at the protein and RNA level has been previously examd. by non-quant. methods such as in situ hybridization, Northern blotting and immunohistochem. To establish an introductory understanding of the quant. mRNA expression of **MT-SP1** and to correlate these levels with urokinase-type plasminogen activator receptor (uPAR), a key component of extracellular proteolysis, quant. RT-PCR was carried out. RNA expression was analyzed in 34 human cancer cell lines, 26 human tissues and 18 primary human breast cancer tissue samples. **MT-SP1** mRNA is highly expressed in many breast, ovarian, prostate and colon cancer cell lines and normal human tissues of endodermal origin. At the transcript level, **MT-SP1** shows a highly statistically significant correlation (Pearson's product moment correlation $r = 0.784$, $p < 0.001$) with uPAR in human breast cancer tissue. The exact role of **MT-SP1** in concert with proteins such as uPAR and other members of the plasminogen activator cascade has yet to be ascertained. However, the significant correlation between **MT-SP1** and uPAR transcript levels in this initial study suggests further work to establish the role of **MT-SP1** as a possible prognostic, diagnostic or therapeutic target for breast cancer.

AN 2003:329809 CAPLUS

TI Quantitation of membrane type **serine protease** 1 (**MT-SP1**) in transformed and normal cells

AU Bhatt, Ami S.; Takeuchi, Toshi; Ylstra, Bauke; Ginzinger, David; Albertson, Donna; Shuman, Marc A.; Craik, Charles S.
CS School of Medicine, University of California at San Francisco, San Francisco, CA, 94143, USA
SO Biological Chemistry (2003), 384(2), 257-266
CODEN: BICHF3; ISSN: 1431-6730
PB Walter de Gruyter GmbH & Co. KG
DT Journal
LA English
RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 32 OF 42 CAPLUS COPYRIGHT 2003 ACS
AB Specific human antibodies targeting proteases expressed on cancer cells can be valuable reagents for diagnosis, prognosis, and therapy of cancer. To this end, a phage-displayed antibody library was screened against a cancer-assocd. **serine protease**, **MT-SP1**. A protein inhibitor of **serine proteases** that binds to a defined surface of **MT-SP1** was used in an affinity-based washing procedure. Six antibodies were selected on the basis of their ELISA profiles and ability to serve as useful immunol. reagents. The apparent Ki, indicative of the potency of the antibodies at inhibiting human **MT-SP1** activity, ranged from 50 pM to 129 nM. Two of the antibodies had approx. 800-fold and 1500-fold selectivity when tested against the most homologous **serine protease** family member, mouse **MT-SP1**, that exhibits 86.6% sequence identity. Surface plasmon resonance was used as an independent means of detg. the binding consts. of the six antibodies. Assocn. rates were as high as 1.15.times.107 s-1 M-1, and dissocn. rates were as low as 3.8.times.10-4 s-1. One antibody was shown to detect denatured **MT-SP1** with no cross reactivity to other family members in HeLa or PC3 cells. Another antibody recognized the enzyme in human prostate tissue samples for immunohistochem. anal. The mode of binding among the six antibodies and the protease was analyzed by competition ELISA using three distinctly different inhibitors that mapped the enzyme surface. These antibodies constitute a new class of highly selective protease inhibitors that can be used to dissect the biol. roles of proteolytic enzymes as well as to develop diagnostic and therapeutic reagents.
AN 2003:8295 CAPLUS
DN 138:165638
TI Potent and Selective Inhibition of Membrane-Type **Serine Protease** 1 by Human Single-Chain Antibodies
AU Sun, Jeonghoon; Pons, Jaume; Craik, Charles S.
CS Department of Pharmaceutical Chemistry, University of California, San Francisco, CA, 94143, USA
SO Biochemistry (2003), 42(4), 892-900
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 33 OF 42 CAPLUS COPYRIGHT 2003 ACS
AB A review on the domain structure and processing of membrane type **serine protease** 1 (**MT-SP1**), tissue distribution of **MT-SP1**, and potential roles of **MT-SP1** in epithelial turnover, apoptosis, tissue repair, and cancer invasion.
AN 2002:740823 CAPLUS
DN 137:243717
TI Transmembrane **serine protease MT-SP1** which regulates metabolism of epithelial cells. Pertaining to tissue

repair and apoptosis on the one hand, aggravating cancer invasion on the other hand
AU Tsuzuki, Satoshi; Fushiki, Tohru
CS Grad. Sch. Agric., Kyoto Univ., Japan
SO Kagaku to Seibutsu (2002), 40(9), 564-565
CODEN: KASEAA; ISSN: 0453-073X
PB Gakkai Shuppan Senta
DT Journal; General Review
LA Japanese

L2 ANSWER 34 OF 42 CAPLUS COPYRIGHT 2003 ACS
AB Matriptase/**MT**-**SP1** is a novel tumor-assocd. type II transmembrane **serine protease** that is highly expressed in the epidermis, thymic stroma, and other epithelia. A null mutation was introduced into the Matriptase/**MT**-**SP1** gene of mice to det. the role of Matriptase/**MT**-**SP1** in epidermal development and neoplasia. Matriptase/**MT**-**SP1**-deficient mice developed to term but uniformly died within 48 h of birth. All epidermal surfaces of newborn mice were grossly abnormal with a dry, red, shiny, and wrinkled appearance. Matriptase/**MT**-**SP1**-deficiency caused striking malformations of the stratum corneum, characterized by dysmorphic and pleomorphic corneocytes and the absence of vesicular bodies in transitional layer cells. This aberrant skin development seriously compromised both inward and outward epidermal barrier function, leading to the rapid and fatal dehydration of Matriptase/**MT**-**SP1**-deficient pups. Loss of Matriptase/**MT**-**SP1** also seriously affected hair follicle development resulting in generalized follicular hypoplasia, absence of erupted vibrissae, lack of vibrissal hair canal formation, ingrown vibrissae, and wholesale abortion of vibrissal follicles. Furthermore, Matriptase/**MT**-**SP1**-deficiency resulted in dramatically increased thymocyte apoptosis, and depletion of thymocytes. This study demonstrates that Matriptase/**MT**-**SP1** has pleiotropic functions in the development of the epidermis, hair follicles, and cellular immune system.
AN 2002:467020 CAPLUS
DN 137:166699
TI Matriptase/**MT**-**SP1** is required for postnatal survival, epidermal barrier function, hair follicle development, and thymic homeostasis
AU List, Karin; Haudenschild, Christian C.; Szabo, Roman; Chen, WanJun; Wahl, Sharon M.; Swaim, William; Engelholm, Lars H.; Behrendt, Niels; Bugge, Thomas H.
CS Oral and Pharyngeal Cancer Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD, 20892, USA
SO Oncogene (2002), 21(23), 3765-3779
CODEN: ONCNES; ISSN: 0950-9232
PB Nature Publishing Group
DT Journal
LA English
RE.CNT 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 35 OF 42 CAPLUS COPYRIGHT 2003 ACS
AB A cDNA encoding a novel **serine protease**, which we designated spinesin, has been cloned from human spinal cord. The longest open reading frame was 457 amino acids. A homol. search revealed that the human spinesin gene was located at chromosome 11q23 and contained 13 exons, the gene structure being similar to that of TMPRSS3 whose gene is also located on 11q23. Spinesin has a simple type II transmembrane structure, consisting of, from the N terminus, a short cytoplasmic domain, a transmembrane domain, a stem region contg. a scavenger receptor-like domain, and a **serine protease** domain. Unlike TMPRSS3,

it carries no low d. lipoprotein receptor domain in the stem region. The extracellular region carries five N-glycosylation sites. The sequence of the protease domain carried the essential triad His, Asp, and Ser and showed some similarity to that of TMPRSS2, hepsin, HAT, **MT-SP1**, TMPRSS3, and corin, sharing 45.5, 41.9, 41.3, 40.3, 39.1, and 38.5% identity, resp. The putative mature protease domain preceded by H6DDDDK was produced in Escherichia coli, purified, and successfully activated by immobilized enterokinase. Its optimal pH was about 10. It cleaved synthetic substrates for trypsin, which is inhibited by p-amidinophenylmethanesulfonyl fluoride hydrochloride but not by antipain or leupeptin. Northern blot anal. against mRNA from human tissues including liver, lung, placenta, and heart demonstrated a specific expression of spinesin mRNA in the brain. Immunohistochem., spinesin was predominantly expressed in neurons, in their axons, and at the synapses of motoneurons in the spinal cord. In addn., some oligodendrocytes were clearly stained. These results indicate that spinesin is transported to the synapses through the axons after its synthesis in the cytoplasm and may play important roles at the synapses. Further analyses are required to clarify its roles at the synapses and in oligodendrocytes.

AN 2002:209550 CAPLUS
DN 137:136759
TI Spinesin/TMPRSS5, a novel transmembrane **serine protease**, cloned from human spinal cord
AU Yamaguchi, Nozomi; Okui, Akira; Yamada, Tatsuo; Nakazato, Hiroshi; Mitsui, Shinichi
CS Department of Cell Biology, Research Institute for Neurological Diseases and Geriatrics, Kyoto Prefectural University of Medicine, Kyoto, 602-8566, Japan
SO Journal of Biological Chemistry (2002), 277(9), 6806-6812
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 36 OF 42 CAPLUS COPYRIGHT 2003 ACS
AB Epithin was originally identified as a mouse type II membrane **serine protease**. Its human orthologue membrane type-**serine protease** 1 (**MT-SP1**)/matriptase has been reported to be localized on the plasma membrane. In addn., sol. forms of matriptase were isolated from human breast milk and breast cancer cell-conditioned medium. In this paper, we report a processing mechanism that appears to be required for the release of epithin. CHO-K1 or COS7 cells transfected with single full-length epithin cDNA generated two different-sized proteins in cell lysates, 110 and 92 kDa. The 92-kDa epithin was found to be an N-terminally truncated form of the 110-kDa epithin, and it was the only form detected in the culture medium. The 92-kDa epithin was also found on the cell surface, where it was anchored by the N-terminal fragment. The results of in vivo cell labeling expts. indicate that the 110-kDa epithin is rapidly processed to the 92-kDa epithin. Using site-directed mutagenesis expts., we identified Gly149 of the GSVIA sequence in epithin as required for the processing and release of the protein. These results suggest that N-terminal processing of epithin at Gly149 is a necessary prerequisite step for release of the protein.

AN 2001:893346 CAPLUS
DN 136:130745
TI N-terminal processing is essential for release of epithin, a mouse type II membrane **serine protease**
AU Cho, Eun-Gyung; Kim, Moon Gyo; Kim, Chungho; Kim, Seung-Ryul; Seong, Ihn Sik; Chung, Chinha; Schwartz, Ronald H.; Park, Dongeun
CS School of Biological Sciences, Seoul National University, Seoul, 151-742, S. Korea

SO Journal of Biological Chemistry (2001), 276(48), 44581-44589
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 37 OF 42 CAPLUS COPYRIGHT 2003 ACS
AB Membrane type-**serine protease** 1 (**MT-SP1**) plays potential roles in the process of invasion and metastasis of carcinomas. In the present study, we cloned a rat **MT-SP1** cDNA and investigated the intestinal distribution and proteolytic properties of the enzyme. By in situ hybridization we found the prominent expression of the mRNA in the epithelial layer of the small intestinal upper villi and of the colon, where cells are loosely attached to the basement membrane. When **MT-SP1** was expressed in Caco-2, a colonic carcinoma cell line, the protein was localized exclusively on the basolateral side. A secreted form of the enzyme produced in COS-1 cells digested fibronectin and laminin. These findings suggest that **MT-SP1** participates in the control of intestinal epithelial turnover by regulating the cell-substratum adhesion. (c) 2001 Academic Press.
AN 2001:709422 CAPLUS
DN 136:83109
TI A Role for Membrane-Type **Serine Protease** (**MT-SP1**) in Intestinal Epithelial Turnover
AU Satomi, Shigeki; Yamasaki, Yoshie; Tsuzuki, Satoshi; Hitomi, Yoshitaka; Iwanaga, Toshihiko; Fushiki, Tohru
CS Laboratory of Nutrition Chemistry, Division of Food Science and Biotechnology, Graduate School of Agriculture, Kyoto University, Kyoto, 606-8502, Japan
SO Biochemical and Biophysical Research Communications (2001), 287(4), 995-1002
CODEN: BBRCA9; ISSN: 0006-291X
PB Academic Press
DT Journal
LA English
RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 38 OF 42 CAPLUS COPYRIGHT 2003 ACS
AB A review on matrix metalloproteinases (MMPs) and urokinase-type plasminogen activator (uPA) in proteolytic degrdn. of the extracellular matrix and basement membrane in cancer invasion and metastasis. Specifically roles of MMP-2 and MMP-9 in proteolytic degrdn. and roles of uPA, uPA receptor, membrane-type matrix metalloproteinases (MT-MMPs), and MMP-3 in regulating MMP activation cascade are discussed. Topics discussed include proteinases in proteolytic degrdn. of the extracellular matrix and basement membrane; matrix metalloproteinases; serine proteinases and membrane type serine proteinase 1 (**MT-SP1**); and clin. application of MMP inhibitors.
AN 2001:677433 CAPLUS
DN 136:292277
TI Cancer invasion and metastasis
AU Okusa, Yasushi; Ichikura, Takashi
CS First Department of Surgery, National Defense Medical College, Japan
SO Igaku no Ayumi (2001), 198(1), 57-61
CODEN: IGAYAY; ISSN: 0039-2359
PB Ishiyaku Shuppan
DT Journal; General Review
LA Japanese

L2 ANSWER 39 OF 42 CAPLUS COPYRIGHT 2003 ACS

AB This invention provides cDNA and encoded amino acid sequences of a novel membrane-type **serine protease** (designated **MT-SP1**) elevated expression of which is assocd. with cancer. In one embodiment, this invention provides a method obtaining a prognosis or of detecting or staging a cancer in an organism. The method involves providing a biol. sample from the organism and detecting the level of a membrane-type **serine protease** 1 (**MT-SP1**) in the sample, where an elevated level of the membrane-type **serine protease**, as compared to the level of the protease in a biol. sample from a normal healthy organism indicates the presence or stage of the cancer.

AN 2001:247459 CAPLUS

DN 134:294083

TI Characterization and diagnostic and therapeutic uses of cancer-associated membrane type **serine protease** 1 (**MT-SP1**)

IN Craik, Charles S.; Takeuchi, Toshihiko; Shuman, Marc

PA The Regents of the University of California, USA

SO PCT Int. Appl., 102 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001023524	A2	20010405	WO 2000-US27250	20001002
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 2000079913	A5	20010430	AU 2000-79913	20001002
PRAI	US 1999-410362	A	19990930		
	WO 2000-US27250	W	20001002		

L2 ANSWER 40 OF 42 CAPLUS COPYRIGHT 2003 ACS

AB Membrane-type **serine protease** 1 (**MT-SP1**) was recently cloned, and we now report its biochem. characterization. **MT-SP1** is predicted to be a type II transmembrane protein with an extracellular protease domain. This localization was exptl. verified using immunofluorescent microscopy and a cell-surface biotinylation technique. The substrate specificity of **MT-SP1** was detd. using a positional scanning-synthetic combinatorial library and substrate phage techniques. The preferred cleavage sequences were found to be (P4-(Arg/Lys)P3-(X)P2-(Ser)P1-(Arg)P1'-(Ala)) and (P4-(X)P3-(Arg/Lys)P2-(Ser)P1(Arg)P1'(Ala)), where X is a non-basic amino acid. Protease-activated receptor 2 (PAR2) and single-chain urokinase-type plasminogen activator are proteins that are localized to the extracellular surface and contain the preferred **MT-SP1** cleavage sequence. The ability of **MT-SP1** to activate PARs was assessed by exposing PAR-expressing Xenopus oocytes to the sol. **MT-SP1** protease domain. The latter triggered calcium signaling in PAR2-expressing oocytes at 10 nM but failed to trigger calcium signaling in oocytes expressing PAR1, PAR3, or PAR4 at 100 nM. Single-chain urokinase-type plasminogen activator was activated using catalytic amts. of **MT-SP1** (1 nM), but plasminogen was not cleaved under similar conditions. The membrane localization of **MT-SP1** and its affinity for these key extracellular substrates suggests a role of the proteolytic activity in regulatory events.

AN 2000:627750 CAPLUS
DN 133:331259
TI Cellular localization of membrane-type **serine protease** 1 and identification of protease-activated receptor-2 and single-chain urokinase-type plasminogen activator as substrates
AU Takeuchi, Toshihiko; Harris, Jennifer L.; Huang, Wei; Yan, Kelly W.; Coughlin, Shaun R.; Craik, Charles S.
CS Department of Pharmaceutical Chemistry and Biochemistry and Biophysics, University of California, San Francisco, CA, 94143, USA
SO Journal of Biological Chemistry (2000), 275(34), 26333-26342
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 41 OF 42 CAPLUS COPYRIGHT 2003 ACS
AB Three novel cDNAs encoding **serine proteases**, that may play a role in early vertebrate development, have been identified from Xenopus laevis. These Xenopus cDNAs encode trypsin-like **serine proteases** and are designated Xenopus embryonic **serine protease** (Xesp)-1, Xesp-2, and XMT-SP1, a homolog of human **MT-SP1**. Xesp-1 is likely to be a secreted protein that functions in the extracellular space. Xesp-2 and XMP-SP1 are likely to be type II membrane proteases with multidomain structures. Xesp-2 has eight low d. lipoprotein receptor (LDLR) domains and one scavenger receptor cysteine-rich (SRCR) domain, and XMT-SP1 has four LDLR domains and two CUB domains. The temporal expressions of these **serine protease** genes show distinct and characteristic patterns during embryogenesis, and they are differently distributed in adult tissues. Overexpression of Xesp-1 caused no significant defect in embryonic development, but overexpression of Xesp-2 or XMT-SP1 caused defective gastrulation or apoptosis, resp. These results suggest that these proteases may play important roles during early Xenopus development, such as regulation of cell movement in gastrulae.
AN 2000:486894 CAPLUS
DN 134:1162
TI Isolation and characterization of three novel **serine protease** genes from Xenopus laevis
AU Yamada, K.; Takabatake, T.; Takeshima, K.
CS Graduate School of Human Informatics, Nagoya University, Nagoya, 464-8601, Japan
SO Gene (2000), 252(1-2), 209-216
CODEN: GENED6; ISSN: 0378-1119
PB Elsevier Science B.V.
DT Journal
LA English

L2 ANSWER 42 OF 42 CAPLUS COPYRIGHT 2003 ACS
AB **Serine proteases** of the chymotrypsin fold are of great interest because they provide detailed understanding of their enzymic properties and their proposed role in a no. of physiol. and pathol. processes. The authors have been developing the macromol. inhibitor ecotin to be a "fold-specific" inhibitor that is selective for members of the chymotrypsin-fold class of proteases. Inhibition of protease activity through the use of wild-type and engineered ecotins results in inhibition of rat prostate differentiation and retardation of the growth of human PC-3 prostatic cancer tumors. In an effort to identify the proteases that may be involved in these processes, reverse transcription-PCR with PC-3 poly(A)+ mRNA was performed by using degenerate oligonucleotide primers. These primers were designed by using conserved protein sequences unique to chymotrypsin-fold **serine proteases**. Five proteases were identified: urokinase-type plasminogen activator, factor XII, protein

C, trypsinogen IV, and a protease that the authors refer to as membrane-type **serine protease** 1 (**MT-SP1**). The cloning and characterization of the **MT-SP1** cDNA shows that it encodes a mosaic protein that contains a transmembrane signal anchor, two CUB domains, four LDLR repeats, and a **serine protease** domain. Northern blotting shows broad expression of **MT-SP1** in a variety of epithelial tissues with high levels of expression in the human gastrointestinal tract and the prostate. A His-tagged fusion of the **MT-SP1** protease domain was expressed in Escherichia coli, purified, and autoactivated. Ecotin and variant ecotins are subnanomolar inhibitors of the **MT-SP1** activated protease domain, suggesting a possible role for **MT-SP1** in prostate differentiation and the growth of prostatic carcinomas.

AN 1999:684470 CAPLUS

DN 132:11272

TI Reverse biochemistry: use of macromolecular protease inhibitors to dissect complex biological processes and identify a membrane-type **serine protease** in epithelial cancer and normal tissue

AU Takeuchi, Toshihiko; Shuman, Marc A.; Craik, Charles S.

CS Departments of Pharmaceutical Chemistry and Biochemistry & Biophysics, University of California, San Francisco, CA, 94143, USA

SO Proceedings of the National Academy of Sciences of the United States of America (1999), 96(20), 11054-11061
CODEN: PNASA6; ISSN: 0027-8424

PB National Academy of Sciences

DT Journal

LA English

RE.CNT 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD
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